**In the United States Patent and Trademark Office
on Appeal from the Examiner to the Board
of Patent Appeals and Interferences**

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| In re Application of: | George D. Purvis III |
| Serial No.: | 10/655,870 |
| Filing Date: | September 5, 2003 |
| Examiner: | Mary K. Zeman |
| Group Art Unit: | 1631 |
| Confirmation No.: | 7307 |
| Title: | *Calculating a Potential of Mean Force (PMF) Score of a Protein-Ligand Complex* |

**MAIL STOP: APPEAL BRIEF-PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

**Appeal Brief**

Appellant has appealed to the Board of Patent Appeals and Interferences from the decision of the Examiner sent electronically 16 April 2007, maintaining the final rejection of Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31, which are all pending in this case. Appellant respectfully submits this Appeal Brief with the statutory fee of $500.00.

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**Real Party in Interest**

Fujitsu Limited currently owns this Application. An assignment recorded 10 August 2004 in the Assignment Records of the United States Patent and Trademark Office at Reel 014966, Frames 0461-0463, indicates that Fujitsu Limited currently owns this Application.

## Related Appeals and Interferences

No known appeals, interferences, or judicial proceedings are related to or will directly affect or have a bearing on the Board's decision on this Appeal. The Board's decision on this Appeal will not affect any known appeals, interferences, or judicial proceedings.

## Status of Claims

Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 are pending in this Application and all stand rejected under the final Office Action sent electronically 4 January 2007. Appellant presents all pending claims for appeal. The attached Claims Appendix shows all pending claims.

## Status of Amendments

The Examiner has entered all amendments submitted by Appellants.

## Summary of Claimed Subject Matter

FIGURE 1 illustrates an example system 10 for calculating a PMF score of a protein-ligand complex. (Page 5, Lines 2-3). System 10 includes a computer system 12 and a PMF-scoring module 14. (Page 5, Lines 3-4). In particular embodiments, a module may include software, hardware, or both. (Page 5, Lines 4-5). Computer system 12 may enable a user to provide input to and receive output from PMF-scoring module 14. (Page 5, Lines 5-6). Computer system 12 may include one or more modules for generating one or more graphical user interfaces (GUIs) for providing input to and receiving output from PMF-scoring module 14. (Page 5, Lines 6-8). PMF-scoring module 14 may calculate one or more PMF scores of one or more protein-ligand complexes specified by a user and return the calculated PMF scores to the user. (Page 5, Lines 8-10). A PMF score of a protein-ligand complex may indicate the binding affinity between the protein and the ligand in the protein-ligand complex, and the binding affinity between the protein and the ligand in the protein-ligand complex may indicate the ability of the ligand to inhibit or otherwise modify the function of the protein. (Page 5, Lines 10-14). PMF-scoring module 14 includes a repulsion-term module 16 that may calculate one or more repulsion terms. (Page 5, Lines 14-16). PMF-scoring module 14 may use PMF-scoring data 18 to calculate a PMF score of a protein-ligand complex. (Page 5, Lines 16-17). PMF-scoring data 18 data that PMF-scoring module 14 may use to calculate a PMF score of a protein-ligand complex. (Page 5, Lines 17-19). In particular embodiments, PMF-scoring data 18 includes empirically derived parameters (such as minimum binding-energy distance and well-depth values) that may be used to calculated a PMF score of a protein-ligand complex. (Page 5, Lines 19-22).

To calculate a PMF score of a protein-ligand complex, PMF-scoring module 14 calculates a PMF score of each protein-ligand atom pair in the protein-ligand complex and combines the calculated PMFs with each other. (Page 5, Lines 29, through Page 6, Line 1). As an example and not by way of limitation, in particular embodiments:

$$\textbf{\textit{PMF Score}} = \sum_{\substack{kl \\ r<r_{cutoff}^{ij}}} A_{ij}(r)$$

$A_{ij}(r)$ is a PMF of a protein-ligand atom pair of atom-pair type *ij* at distance *r*, and *kl* is a protein-ligand atom pair of atom-pair type *ij*. (Page 6, Lines 1-5). A protein-ligand atom pair of atom-pair type *ij* includes a first atom of protein atom type *i* and a second atom of ligand atom type *j*. (Page 6, Lines 5-7). A PMF of a protein-ligand atom pair corresponds to

interaction energy between the two atoms in the protein-ligand atom pair. (Page 6, Lines 7-8). For purposes of calculating PMFs of protein-ligand atom pairs, protein atoms are defined by protein atom type and ligand atoms are defined by ligand atom type. (Page 6, Lines 8-10). Atom type is defined by element (carbon, oxygen, hydrogen, etc.) and local bonding environment (polar aliphatic, nonpolar aliphatic, polar aromatic, nonpolar aromatic, hydrogen bond donor, hydrogen bond acceptor, etc.). (Page 6, Lines 10-13). Examples of ligand atom types include nonpolar carbon $sp^3$ aliphatic; polar $sp^3$ carbon bonded to an atom other than carbon or hydrogen; sp nitrogen bound to one carbon; and other suitable ligand atom types. (Page 6, Lines 13-15). Examples of protein atom types include nonpolar aliphatic carbon; polar aliphatic $sp^2$ or $sp^3$ carbon bonded to atoms other than carbon or hydrogen; positively charged nitrogen; sulfur as hydrogen bond acceptor; nitrogen in a planar ring structure; and other suitable protein atom types. (Page 6, Lines 16-19). In particular embodiments, there may be thirty-four ligand atom types and sixteen protein atom types. (Page 6, Lines 19-20). Herein, reference to atom type includes protein atom type, ligand atom type, or both, where appropriate. (Page 6, Lines 20-21).

PMFs of protein-ligand atom pairs are derived from application of one or more atom-pair distribution functions to data that describes analyzed protein-ligand complexes, such as data from the BROOKHAVEN PROTEIN DATA BANK (PDB) or the PDB maintained by the RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATCIS (RCSB). (Page 6, Lines 22-26). As an example and not by way of limitation, in particular embodiments:

$$A_{ij} = -k_B T \ln\left[ f^{j}_{vol\_corr}(r) \frac{\rho^{ij}_{seg}(r)}{\rho^{ij}_{bulk}} \right] = -k_B T \ln \rho^{ij}_{seg}(r) - k_B T \ln f^{j}_{vol\_corr}(r) + k_B T \ln \rho^{ij}_{bulk}$$

$k_B$ is a Boltzmann factor, $T$ is absolute temperature, $f^{j}_{vol\_corr}(r)$ is a ligand volume-correction factor, and $\rho^{ij}_{bulk}$ is a number density of atom-pair type $ij$ occurrences at a certain distance. (Page 6, Line 26, through Page 7, Line 5). In particular embodiments, to account for short-distance interaction between two atoms in a protein-ligand atom pair, a repulsion term is used to calculate a PMF of the protein-ligand atom pair. (Page 7, Lines 5-7). As an example and not by way of limitation, in particular embodiments, if two atoms in a protein-ligand atom pair of atom-pair type $ij$ are separated from each other by a distance that is shorter than the

longest distance without an occurrence of atom-pair type *ij* in data that describes analyzed protein-ligand complexes, a repulsion term is incorporated into the above formula. (Page 7, Lines 7-11). In particular embodiments, if short-distance interaction between two atoms in a protein-ligand atom pair is greater than 4 kcal/mol, the above formula is replaced by a repulsion term. (Page 7, Lines 11-14).

A repulsion term corresponds to repulsive force between two atoms in a protein-ligand atom pair. (Page 7, Lines 15-16). Repulsive force causes two atoms in a protein-ligand atom pair to repel each other and may result from van der Waals (VDW) potential, electrostatic potential, and hydrogen bond potential between the two atoms. (Page 7, Lines 16-18). Although repulsive force is described as resulting from particular potentials, the present invention contemplates repulsive force resulting from any suitable combination of any suitable potentials. (Page 7, Lines 18-21). In particular embodiments, a repulsion term used to calculate a PMF of a protein-ligand atom pair is calculated according to (1) a minimum binding-energy distance of the protein-ligand atom pair and (2) a well depth of the protein-ligand atom pair. (Page 7, Lines 21-24). A minimum binding-energy distance of a protein-ligand atom pair is a distance between the two atoms in the protein-ligand atom pair that corresponds to a minimum binding energy between the two atoms in the protein-ligand atom pair. (Page 7, Lines 24-26). A well depth of a protein-ligand atom pair corresponds to an amount of binding interaction between the two atoms in the protein-ligand atom pair. (Page 7, Lines 27-28).

In traditional PMF scoring, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, a minimum binding-energy distance value is used that corresponds to a sum of VDW radii of the two atoms in the protein-ligand atom pair. (Page 8, Lines 1-4). In addition, in traditional PMF scoring, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, a well-depth value is used that corresponds to atom hardnesses of the two atoms in the protein-ligand atom pair. (Page 8, Lines 4-7). VDW radii account for VDW potentials, but do not account for other potentials (such as electrostatic potential and hydrogen bond potential) that may cause repulsive force, as described above. (Page 8, Lines 7-9). As a result, traditional PMF scoring does not account for potentials other than VDW potential that may cause repulsive force and, therefore, often generates inaccurate PMF scores of protein-ligand complexes. (Page 8, Lines 9-11).

In contrast, in particular embodiments of the present invention, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may use a minimum binding-energy distance value that corresponds to an empirically derived minimum binding-energy distance value. (Page 8, Lines 12-15). In particular embodiments, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may use a well-depth value that corresponds to an empirically derived well-depth value. (Page 8, Lines 15-18). In particular embodiments, each atom-pair type may correspond to an empirically derived minimum binding-energy distance value and an empirically derived well-depth value. (Page 8, Lines 18-20). To calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may determine an atom-pair type of the protein-ligand atom pair, access an empirically derived minimum binding-energy distance value and an empirically derived well-depth value that correspond to the determined atom-pair type, and use the accessed values to calculate the PMF of the protein-ligand atom pair. (Page 8, Lines 21-26).

FIGURE 3 illustrates an example method for calculating a PMF score of a protein-ligand complex. (Page 13, Lines 5-6). The method begins at step 100, where a user at computer system 12 specifies a protein-ligand complex for PMF scoring. (Page 13, Lines 6-7). At step 102, PMF-scoring module 14 accesses PMF-scoring data 18 associated with the specified protein-ligand complex. (Page 13, Lines 7-9). PMF-scoring data 18 may describe the protein and the ligand in the specified protein-ligand complex. (Page 13, Lines 9-10). As an example, PMF-scoring data 18 may describe the number of atoms and the type and position of each atom in the protein. (Page 13, Lines 10-11). As another example, PMF-scoring data 18 may describe the number of atoms and the type and position of each atom in the ligand. (Page 13, Lines 12-13). At step 104, PMF-scoring module 14 identifies a protein-ligand atom pair in the specified protein-ligand complex. (Page 13, Lines 13-14). At step 106, if a repulsion term should be used to calculate a PMF of the identified protein-ligand atom pair, the method proceeds to step 108. (Page 13, Lines 14-16).

At step 108, PMF-scoring module 14 accesses a table 30 of empirically derived minimum binding-energy distance and well-depth values. (Page 13, Lines 17-18). PMF-scoring data 18 may include table 30. (Page 13, Lines 18-19). At step 110, PMF-scoring module 14 uses table 30 to determine a minimum binding-energy distance value and a well-

depth value that correspond to the identified protein-ligand atom pair. (Page 13, Lines 19-21). At step 112, PMF-scoring module 14 uses the determined minimum binding-energy distance and well-depth values to calculate a repulsion term. (Page 13, Lines 21-23). At step 114, PMF-scoring module 14 uses the calculated repulsion term to calculate a PMF of the identified protein-ligand atom pair, at which point the method proceeds to step 118. (Page 13, Lines 23-25). At step 106, if a repulsion term should not be used to calculate a PMF of the identified protein-ligand atom pair, the method proceeds to step 116. (Page 13, Lines 25-27).

At step 116, PMF-scoring module 14 calculates a PMF of the identified protein-ligand atom pair without a repulsion term. (Page 13, Lines 28-29). At step 118, if a PMF of a protein-ligand atom pair in the specified protein-ligand complex has not been calculated, the method returns to step 104. (Page 13, Line 29, through Page 14, Line 1). At step 118, if a PMF of each protein-ligand atom pair in the specified protein-ligand complex has been calculated, the method proceeds to step 120. (Page 14, Lines 1-3). At step 120, PMF-scoring module 14 uses the calculated PMFs of the protein-ligand atom pairs in the specified protein-ligand complex to calculate a PMF score of the specified protein-ligand complex. (Page 14, Lines 3-5). At step 122, PMF-scoring module 14 communicates the calculated PMF score to the user at computer system 12, at which point the method ends. (Page 14, Lines 5-7).

Particular embodiments of the present invention may provide one or more technical advantages. (Page 3, Lines 14-15). Particular embodiments may be used to more accurately predict a structure of a protein-ligand complex. (Page 3, Lines 15-16). Particular embodiments may be used to more accurately calculate a binding affinity between a protein and a ligand and the positions of the atoms in the protein-ligand complex, which may help determine a mode of action of a ligand. (Page 3, Lines 16-19). Particular embodiments may be used to calculate a more accurate PMF score of a protein-ligand complex. (Page 3, Lines 19-20). In particular embodiments, a PMF score of a protein-ligand complex may be calculated according to more accurate PMF potentials that each account for multiple potentials (such as a van der Waals potential, an electrostatic potential, and a hydrogen bonding potential) that may cause repulsive force in a protein-ligand atom pair. (Page 3, Lines 20-24). Particular embodiments may be used to calculate a more accurate PMF potential between two atoms in a protein-ligand atom pair. (Page 3, Lines 24-25).

For the convenience of the Board, Appellants provide the following mappings of the claims here on appeal. Appellants do not necessarily identify all portions of the Specification and Drawings relevant to the recited elements of the claims. Appellants provide the following mapping not to limit the scope of the claims, but to help the Board make a decision on this Appeal.

Independent Claim 1 recites the following:

> An apparatus comprising:
> one or more processors; (e.g.: Figure 1; Page 5, Lines 2-28) and
> a memory coupled to the processors comprising one or more instructions, (e.g.: Figure 1; Page 5, Lines 2-28) the processors operable when executing the instructions to:
>
> determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex; (e.g.: Page 5, Line 29, through Page 6, Line 21)
>
> calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type; (e.g.: Page 6, Line 22, through Page 8, Line 26)
>
> calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; (e.g.: Page 6, Line 22, through Page 8, Line 26) and
>
> calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex. (e.g.: Page 5, Line 29, through Page 6, Line 21)

Independent Claims 11, 21, and 31 are similar to independent Claim 1.

**Grounds of Rejection for Review on Appeal**

Appellant requests the Board to review the Examiner's final rejection of Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. § 101 as being directed to nonstatutory subject matter. Appellant also requests the Board to review Examiner's final rejection of Independent Claim 31 under 35 U.S.C. § 112, second paragraph, as being indefinite.

## Argument

For at least the following reasons, the Examiner's rejection of Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 is improper and the Board should reverse the Examiner's rejection.

### The Claims Recite Patentable Subject Matter

The Examiner rejects Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31 under 35 U.S.C. § 101 as being directed to nonstatutory subject matter. According to the Examiner, "The system does not produce or output any result that is concrete, tangible and useful. Nothing tangibly embodies in the real world. The result is an abstract idea which must be further manipulated or interpreted to be useful." Appellant disagrees with the Examiner. The ***PMF score of the protein-ligand complex*** resulting from the calculations recited in independent Claims 1, 11, 21, and 31 indicates ***a binding affinity between a protein and a ligand in the protein-ligand complex***, as recited in independent Claims 1, 11, 21, and 31, which is clearly useful, concrete, and tangible under governing Federal Circuit case law.

In *Arrhythmia Research Technology Inc. v. Corazonix Corp.*, the Federal Circuit found that the following claims both recited statutory subject matter under 35 U.S.C. § 101:

> 1. A method for analyzing electrocardiograph signals to determine the presence or absence of a predetermined level of high frequency energy in the late QRS signal, comprising the steps of:
>
> converting a series of QRS signals to time segments, each segment having a digital value equivalent to the analog value of said signals at said time;
>
> applying a portion of said time segments in reverse time order to high pass filter means;
>
> determining an arithmetic value of the amplitude of the output of said filter; and
>
> comparing said value with said predetermined level.
>
> 7. Apparatus for analyzing electrocardiograph signals to determine the level of high frequency energy in the late QRS signal comprising:
>
> means for converting X, Y, and Z lead electrocardiographic input signals to digital valued time segments;
>
> means for examining said X, Y, and Z digital valued time segments and selecting therefrom the QRS waveform portions thereof;

> means for signal averaging a multiplicity of said selected QRS waveforms for each of said X, Y, and Z inputs and providing composite, digital X, Y, and Z QRS waveforms;
>
> high pass filter means;
>
> means for applying to said filter means, in reverse time order, the anterior portion of each said digital X, Y, and Z waveform; and
>
> means for comparing the output of said filter means with a predetermined level to obtain an indication of the presence of a high frequency, low level, energy component in the filter output of said anterior portions.

958 F.2d 1053, 1055, 1059-61, 22 U.S.P.Q.2d 1033, 1035, 1038-39 (Fed. Cir. 1992).

Regarding the method claim, the Federal Circuit stated:

> These claimed steps of "converting," "applying," "determining," and "comparing" are physical process steps that transform one physical, electrical signal into another. The view that there is nothing necessarily physical about signals is incorrect. The *Freeman-Walter-Abele* standard is met, for the steps of Simson's claimed method comprise an otherwise statutory process whose mathematical procedures are applied to physical process steps.

*Arrhythmia Research*, 958 F.2d at 1059, 22 U.S.P.Q.2d at 1038 (citations omitted).

Regarding the apparatus claim, the Federal Circuit stated:

> The Simson apparatus claims thus define a combination of interrelated means for performing specified functions. The computer-performed operations transform a particular input signal to a different output signal, in accordance with the internal structure of the computer as configured by electronic instructions. The claimed invention converts one physical thing into another physical thing just as any other electrical circuitry would do.
>
> . . . .
>
> Corazonix argues that the final output of the claimed apparatus (and process) is simply a number, and that *Benson* and *Flook* support the position that when the end product is a number, the claim is nonstatutory and can not be saved by claim limitations of the use to which this number is put. However, the number obtained is not a mathematical abstraction; it is a measure in microvolts of a specified heart activity, an indicator of the risk of ventricular tachycardia. That the product is numerical is not a criterion of whether the claim is directed to statutory subject matter.
>
> The Simson apparatus claims satisfy the criteria for statutory subject matter. They are directed to a specific apparatus of practical utility and specified application, and meet the requirements of 35 U.S.C. § 101.

*Arrhythmia Research*, 958 F.2d at 1060-61, 22 U.S.P.Q.2d at 1039 (citations omitted).

Thus, as the Federal Circuit later noted in *State Street Bank & Trust Co. v. Signature Financial*, "the transformation of electrocardiograph signals from a patient's heartbeat by a machine through a series of mathematical calculations constitute[s] a practical application of an abstract idea (a mathematical algorithm, formula, or calculation) because it correspond[s] to a useful, concrete, or tangible thing—the condition of a patient's heart." 149 F.3d 1368, 1373, 47 U.S.P.Q.2d 1596, 1601 (Fed. Cir. 1998) (discussing *Arrhythmia Research*). Moreover, "data, transformed by a machine through a series of mathematical calculations to produce a smooth waveform display on a rasterizer monitor, constitute[s] a practical application of an abstract idea (a mathematical algorithm, formula, or calculation) because it produced 'a useful, concrete and tangible result'—the smooth waveform." *Id.* (discussing *In re Allapat*, 33 F.3d 1526, 31 U.S.P.Q.2d 1545 (Fed. Cir. 1994)). Furthermore, "the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation because it produces 'a useful, concrete and tangible result'—a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades." *Id.*

In *AT&T Corp. v. Excel Communications, Inc.*, the Federal Circuit held that the following claim "comfortably falls within the scope of § 101":

> A method for use in a telecommunications system in which interexchange calls initiated by each subscriber are automatically routed over the facilities of a particular one of a plurality of interexchange carriers associated with that subscriber, said method comprising the steps of:
>
> generating a message record for an interexchange call between an originating subscriber and a terminating subscriber, and
>
> including, in said message record, a primary interexchange carrier (PIC) indicator having a value which is a function of whether or not the interexchange carrier associated with said terminating subscriber is a predetermined one of said interexchange carriers.

172 F.3d 1352, 1354, 1358 (Fed. Cir. 1999). According to the Federal Circuit, the "claimed process employs subscribers' and call recipients' PIC [indicators] as data, applies Boolean algebra to those data to determine the value of the PIC indicator, and applies that value through switching and recording mechanisms to create a signal useful for billing purposes."

*Id.* at 1358. The Federal Circuit then went on to hold that the claim at issue was directed to statutory subject matter because "the claimed process applies the Boolean principle to produce a useful, concrete, tangible result without pre-empting other uses of the mathematical principle." *Id.* According to the Federal Circuit, the "useful, concrete, tangible result" of the claimed process was the claimed PIC indicator, which "represents information about the call recipient's PIC, a useful, non-abstract result that facilitates differential billing of long-distance calls made by an IXC's subscriber." *Id.*

Appellant submits that the ***PMF score of the protein-ligand complex*** resulting from the calculations recited in independent Claims 1, 11, 21, and 31 of this Application, which indicates ***a binding affinity between a protein and a ligand in the protein-ligand complex***, as recited in independent Claims 1, 11, 21, and 31, is no less useful, concrete, or tangible than electrocardiograph signals from a patient's heartbeat transformed by a machine through a series of mathematical calculations., a smooth waveform display on a rasterizer monitor, a final share price momentarily fixed for recording and reporting purposes, or information about the primary interexchange carrier of a call recipient for differential billing of long-distance telephone calls.

For at least the above reasons, independent Claims 1, 11, 21, and 31 recite patentable subject matter under 35 U.S.C. § 101. Accordingly, the Board should reverse the Examiner's rejection of independent Claims 1, 11, 21, and 31 and all their dependent claims and instruct the Examiner to issue a notice of allowance of the same.

**Independent Claim 31 is Definite**

The Examiner rejects independent Claim 31 under 25 U.S.C. § 112, second paragraph, as being indefinite. According to the Examiner, "In claim 31, it is entirely unclear what the system comprises. No hardware of any sort is set forth in the claim and the specification does not set forth any particular definition for a system. Claim 31 merely requires a module capable of performing a particular calculation. There are no means for inputting or outputting any information. There is no hardware, memory, processor, etc. associated with the system." Appellant disagrees with the Examiner.

Independent Claim 31 of this Application recites:

A system comprising:
means for determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;
means for calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;
means for calculating a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and
means for calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

Appellant submits that Claim 31 does not recite any modules.

Moreover, the Specification provides the following description:

FIGURE 1 illustrates an example system 10 for calculating a PMF score of a protein-ligand complex. System 10 includes a computer system 12 and a PMF-scoring module 14. In particular embodiments, a module may include software, hardware, or both. Computer system 12 may enable a user to provide input to and receive output from PMF-scoring module 14. Computer system 12 may include one or more modules for generating one or more graphical user interfaces (GUIs) for providing input to and receiving output from PMF-scoring module 14. PMF-scoring module 14 may calculate one or more PMF scores of one or more protein-ligand complexes specified by a user and return the calculated PMF scores to the user. A PMF score of a protein-ligand complex may indicate the binding affinity between the protein and the ligand in the protein-ligand complex, and the binding affinity between the protein and the ligand in the protein-ligand complex may indicate the ability of the ligand to inhibit or otherwise modify the function of the protein. PMF-scoring module 14 includes a repulsion-term module 16 that may calculate one or more repulsion terms, as described below. PMF-scoring module 14 may use PMF-scoring data 18 to calculate a PMF score of a protein-ligand complex. PMF-scoring data 18 data that PMF-scoring module 14 may use to calculate a PMF score of a protein-ligand complex. In particular embodiments, PMF-scoring data 18 includes empirically derived parameters (such as minimum binding-energy distance and well-depth values) that may be used to calculated a PMF score of a protein-ligand complex, as described below. Although components of system 10 are described and illustrated as being separate from each other, the present invention also

> contemplates any suitable components of system 10 being combined with any other suitable components in any suitable manner. As an example and not by way of limitation, in particular embodiments, PMF-scoring module 14 is executed at computer system 12. As another example, in particular embodiments, PMF-scoring data 18 is stored at computer system 12.

(Page 5, Lines 2-28). The Specification provides further descriptions of system 10, computer system 12, PMF-scoring module 14, repulsion-term module 16, and PMF-scoring data 18 and their collective and individual functionality. In particular embodiments, system 10, computer system 12, PMF-scoring module 14, repulsion-term module 16, PMF-scoring data 18, or a combination of two or more such structures perform functions recited in Claim 31.

Furthermore, Appellant submits that, contrary to the Examiner's assertions, independent Claim 31 need not recite "means for inputting or outputting any information" or "hardware, memory, processor, etc. associated with the system" to be definite under 35 U.S.C. § 112, second paragraph.

For at least the above reasons, independent Claim 31 is definite under 35 U.S.C. § 112, second paragraph. Accordingly, the Board should reverse the Examiner's rejection of independent Claim 31 and instruct the Examiner to issue a notice of allowance of the same.

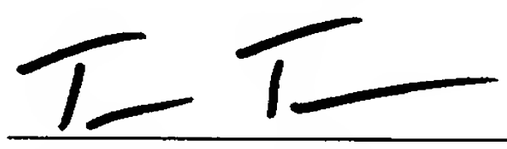
## Conclusion

Appellant has demonstrated that the pending claims are clearly allowable. Appellant respectfully requests the Board of Patent Appeals and Interferences to reverse the Examiner's final rejection of the pending claims and instruct the Examiner to issue a notice of allowance of the same.

Please charge $120.00 for a one-month extension of time and $500.00 for this Appeal Brief to Deposit Account No. 02-0384 of Baker Botts LLP. The Commissioner is authorized to charge any fee and credit any overpayment to Deposit Account No. 02-0384 of BAKER BOTTS L.L.P.

Respectfully submitted,

BAKER BOTTS L.L.P.
Attorneys for Appellants



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Date: 9 July 2007

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## Claims Appendix

1. An apparatus comprising:

one or more processors; and

a memory coupled to the processors comprising one or more instructions, the processors operable when executing the instructions to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;

calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;

calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and

calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

2. The apparatus of Claim 1, wherein the minimum binding-energy distance value of the atom-pair type is an empirically derived minimum binding-energy distance value of the atom-pair type and the well-depth value of the atom-pair type is an empirically derived well-depth value of the atom-pair type.

3-4 (Canceled)

5. The apparatus of Claim 2, wherein a first set of empirically derived minimum binding-energy distances and well-depth values comprises the minimum binding-energy distance value and the well-depth value of the atom-pair type, the first set yielding a better agreement with a plurality of actual analyzed protein-ligand atom pairs than one or more second sets of empirically derived minimum binding-energy distances and well-depth values.

6. (Canceled)

7. The apparatus of Claim 5, wherein root mean square (RMS) deviation between actual analyzed protein-ligand complex structures and protein-ligand complex structures predicted according to a set of empirically derived minimum binding-energy distances and well-depth values determines agreement between the set of empirically derived minimum binding-energy distances and well-depth values and the actual analyzed protein-ligand atom pairs.

8. (Canceled)

9. The apparatus of Claim 5, wherein one or more of the first set of empirically derived minimum binding-energy distances and well-depth values or second sets of empirically derived minimum binding-energy distances and well-depth values are each a product of one or more manual processes or automatic processes.

10. The apparatus of Claim 9, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

11. A method comprising:

determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;

calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;

calculating a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and

calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

12. The method of Claim 11, wherein the minimum binding-energy distance value of the atom-pair type is an empirically derived minimum binding-energy distance value of the atom-pair type and the well-depth value of the atom-pair type is an empirically derived well-depth value of the atom-pair type.

13-14 (Canceled)

15. The method of Claim 12, wherein a first set of empirically derived minimum binding-energy distances and well-depth values comprises the minimum binding-energy distance value and the well-depth value of the atom-pair type, the first set yielding a better agreement with a plurality of actual analyzed protein-ligand atom pairs than one or more second sets of empirically derived minimum binding-energy distances and well-depth values.

16. (Canceled)

17. The method of Claim 15, wherein root mean square (RMS) deviation between actual analyzed protein-ligand complex structures and protein-ligand complex structures predicted according to a set of empirically derived minimum binding-energy distances and well-depth values determines agreement between the set of empirically derived minimum binding-energy distances and well-depth values and the actual analyzed protein-ligand atom pairs.

18. (Canceled)

19. The method of Claim 5, wherein one or more of the first set of empirically derived minimum binding-energy distances and well-depth values or second sets of empirically derived minimum binding-energy distances and well-depth values are each a product of one or more manual processes or automatic processes.

20. The method of Claim 19, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

21. Logic encoded in one or more media for execution and when executed operable to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;

calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;

calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and

calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

22. The logic of Claim 21, wherein the minimum binding-energy distance value of the atom-pair type is an empirically derived minimum binding-energy distance value of the atom-pair type and the well-depth value of the atom-pair type is an empirically derived well-depth value of the atom-pair type.

23-24 (Canceled)

25. The logic of Claim 22, wherein a first set of empirically derived minimum binding-energy distances and well-depth values comprises the minimum binding-energy distance value and the well-depth value of the atom-pair type, the first set yielding a better agreement with a plurality of actual analyzed protein-ligand atom pairs than one or more second sets of empirically derived minimum binding-energy distances and well-depth values.

26. (Canceled)

27. The logic of Claim 25, wherein

root mean square (RMS) deviation between actual analyzed protein-ligand complex structures and protein-ligand complex structures predicted according to a set of empirically derived minimum binding-energy distances and well-depth values determines agreement between the set of empirically derived minimum binding-energy distances and well-depth values and the actual analyzed protein-ligand atom pairs.

28. (Canceled)

29. The logic of Claim 25, wherein one or more of the

first set of empirically derived minimum binding-energy distances and well-depth values or second sets of empirically derived minimum binding-energy distances and well-depth values are each a product of one or more manual processes or automatic processes.

30. The logic of Claim 29, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

31. A system comprising:

means for determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex;

means for calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type;

means for calculating a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and

means for calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

## Evidence Appendix

**NONE**

## Related Proceedings Appendix

**NONE**